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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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TOWNSEND AND TOWNSEND AND CREW, LLP
TWO EMBARCADERO CENTER
EIGHTH FLOOR
SAN FRANCISCO, CA 94111-3834

EXAMINER

EPPERSON, JON D

ART UNIT PAPER NUMBER

1639

DATE MAILED: 03/09/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/668,778	Applicant(s) BALINT ET AL.	
	Examiner Jon D. Epperson	Art Unit 1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 22 December 2005.
2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 63-74 is/are pending in the application.
4a) Of the above claim(s) 64 and 68-70 is/are withdrawn from consideration.
5) ☐ Claim(s) _____ is/are allowed.
6) ☒ Claim(s) 63,65-67 and 71 is/are rejected.
7) ☒ Claim(s) 72-74 is/are objected to.
8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Status of the Application

1. The Response filed December 22, 2005 is acknowledged.
2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior office action.

Status of the Claims

3. Claims 63-74 were pending. No claims were added, amended or canceled. Therefore, claims 63-74 are currently pending.
4. Claims 64 and 68-70 are drawn to non-elected species and/or inventions and thus these claims remain withdrawn from further consideration by the examiner, 37 CFR 1.142(b), there being no allowable generic claim.
3. Therefore, claims 63, 65-67 and 71-74 are examined on the merits in this action.

Withdrawn Objections/Rejections

5. The objections to the specification and abstract are withdrawn in view of Applicants' amendments. All other rejections are maintained and the arguments are addressed below.

Outstanding Objections and/or Rejections

Claim Rejections - 35 USC § 103

6. Claims 63, 65 and 71 are rejected under 35 U.S.C. 103(a) as being unpatentable over Michnick et al. (U.S. Patent No. 6,270,964 B1) (Filing date is **February 2, 1998**) (9/22/03 IDS Ref. AB) and Blau et al. (WO 98/44350) (Date of **October 8, 1998**) (9/22/03 IDS Ref. AG) and Pieper et al. (Piper, U.; Hayakawa, K.; Li, Z., Herzberg, O. "Circularly Permuted β -lactamase from *Staphylococcus aureus* PC1" *Biochemistry* **1997**, 36, 8767-8774) (9/22/03 IDS Ref. BI).

For **claim 63**, Michnick et al. (see entire document) teach protein fragment complementation systems and method of use (e.g., see Michnick et al., abstract and claims; see also column 7, last paragraph), which renders Applicants' claimed invention obvious. Michnick et al. teach a genus of fragment complementation fusion polypeptides that encompasses Applicants' claimed invention (or at least overlaps in scope to a large extent). For example, Michnick et al. disclose a protein "fragment complementation" system comprising a "first fusion product" and a "second fusion product" (i.e., a system) that contains two enzyme fragments (that encompass the two currently claimed β -lactamase fragments) and also two molecular domains that are roughly equivalent in scope to the claimed interactor domains (e.g., see Michnick et al., claim 1; see also figure 1; see also Examples). Michnick et al. also disclose the "reconstitution" of said first and second interactor domains to yield a functional enzyme (e.g., see claim 1, "wherein reassembly of the enzyme fragments ... is detected by means of reconstitution of activity of said enzyme"; see also figure 1).

For **claim 71**, Michnick et al. also teach the use of short peptide linkers (e.g., see column 4, paragraph 1, “One particular strategy for designing a protein complementation assay (PCA) is based on ... resulting new N- and C-termini should be on the same face of the protein [e.g., enzyme] to avoid the need for long peptide linkers [i.e., short peptide linkers are preferred] and allow for studies of orientation-dependence of protein binding”; see also figure 2 and Examples wherein a short flexible polypeptide linker was used with the DHFR PCA).

The prior art teachings of Michnick et al. differ from the claimed invention as follows:

For **claim 63**, Michnick et al. are deficient in that they do not specifically teach the use of the “Class A β -lactamase” enzyme. Michnick et al. only teach the use of enzymes “in general” (e.g., see claim 1; see also column 8, lines 18-21, “It should be understood that the instant invention is not limited to the PCAs presented here, as numerous other enzymes can be selected and used in accordance with the teachings of the present invention”; see also abstract wherein examples like murine dihydrofolate reductase (DHFR) are provided). Michnick also provide further guidance that “teaches toward” Applicants’ claimed β -lactamase (e.g., see Michnick et al., paragraph bridging columns 9-10, “In designing a protein-fragment complementation assay (PCA), we sought to identify an enzyme for which the following is true: 1) An enzyme that is relatively small and monomeric [this is true for β -lactamase], 2) for which structural and functional information exists [this is true for β -lactamase], 3) for which simple assays exist for both *in vivo* and *in vitro* measurement [this is true for β -lactamase], and 4) for

which overexpression in eukaryotic and prokaryotic cells has been demonstrated [this is true for β -lactamase]”).

For *claim 65*, Michnick et al. fail to disclose a fragment complementation system wherein said first and second class A β -lactamase protein break-points are within 10 amino acids in either direction from a junction between 2 amino acid residues of a loop between elements of secondary structure.

However, the combined references of Blau et al. and Pieper et al. teach the following limitations that are deficient in Michnick et al.:

For *claim 63*, the combined references of Blau et al. and Pieper et al. (e.g., see entire documents) teach the use of a β -lactamase in a complementation systems like the one disclosed by Michnick et al. (e.g., see Blau et al., claim 21, “providing a reporter system comprising: a first component comprising a first low affinity reporter subunit, coupled to the first putative binding moiety, and a second component comprising a second low affinity reporter subunit coupled to the second putative binding moiety”; see also page 22, first full paragraph, “In one embodiment of the invention, the reporter subunits comprise an Enzyme ... Exemplary enzymes include ... β -lactamase”; see also page 14, lines 11-18; see also page 11, lines 21-24”). In addition, the combined references of Blau et al. and Pieper et al teach the exact point at which a “class A” β -lactamase can be cleaved to form N-terminal and C-terminal fragments and yet still retain biological activity (e.g., see Pieper et al., abstract wherein the cp254 that was “cleaved in a loop remote from the domain interface” retained “similar” activity to the wild-type β -lactamase; see also cp228 construct, which shows rates that are 0.5-1% of the native

enzyme against some substrates and 10-fold faster than the wild type against a third generation cephalosporin).

For *claim 65*, the combined teachings of Blau et al. and Pieper et al. disclose a break-point within two amino acid residues of a loop between elements of secondary structure (e.g., see Pieper et al., abstract, “The first construct, termed cp254, was cleaved in a loop remote from the domain interface”; see also figure 1; see also Materials and Methods).

For *claim 71*, the combined teachings of Blau et al. and Pieper et al. also disclose a flexible linker between 3-30 amino acids in length (e.g., see Blau et al., pages 16-17, Linking of the Reporter Subunit and the Binding Moiety section, especially, page 16, lines 18-21; see also Pieper et al. figure 1 showing short peptide linker).

It would have been *prima facie* obvious to one skilled in the art at the time the invention was made to use a class A β -lactamase enzyme as taught by the combined teachings of Blau et al. and Pieper et al. with the complementation systems as disclosed by Michnick et al. because Michnick et al. teach a general methodology for producing and/or using a complementation system and the combined teachings of Blau et al. and Pieper et al. explicitly state that a β -lactamase can be used for this purpose (e.g., see Blau et al., page 22, first full paragraph, “In one embodiment of the invention, the reporter subunits comprise an Enzyme ... Exemplary enzymes include ... β -lactamase”).

Furthermore, one of ordinary skill in the art would have been motivated to use the a class A β -lactamase because Michnick et al. state, “In designing a protein-fragment complementation assay (PCA), we sought [i.e., were motivated] to identify an enzyme for

which the following is true: 1) An enzyme that is relatively small and monomeric, 2) for which structural and functional information exists, 3) for which simple assays exist for both *in vivo* and *in vitro* measurement, and 4) for which overexpression in eukaryotic and prokaryotic cells has been demonstrated” (e.g., see Michnick et al., paragraph bridging columns 9-10), which are factors that all point toward the class A β -lactamase (see above). In addition, Pieper et al. demonstrate that a high degree of activity is retained upon fragmentation of the enzyme for constructs like cp254 and a range of activities for constructs like cp228 depending on the nature of the substrate (e.g., see Pieper, abstract, wherein the cp254 construct activity is disclosed as being “very similar” to the wild type; see also page 8773, column 1, Enzymatic Activity section). Finally, one of ordinary skill in the art would have reasonably expected to be successful because Blau et al. explicitly state that a β -lactamase can be used in complementation systems (e.g., see Blau et al., page 22, first full paragraph, “In one embodiment of the invention, the reporter subunits comprise an Enzyme ... Exemplary enzymes include ... β -lactamase”) and Pieper et al. provide explicit examples showing that a class A β -lactamase may be “functionally reconstituted” (e.g., see Pieper et al., abstract, cp254 and cp228 constructs). In addition, Michnick et al. state, “It should be understood that the instant invention is not limited to the PCAs presented here, as numerous other enzymes can be selected and used in accordance with the teachings of the present invention” (e.g., see also column 8, lines 18-21), which would encompass a β -lactamase.

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7. Claims 63, 65, 66 and 71 are rejected under 35 U.S.C. 103(a) as being unpatentable over Michnick et al. (U.S. Patent No. 6,270,964 B1) (Filing date is **February 2, 1998**) (9/22/03 IDS Ref. AB) and Blau et al. (WO 98/44350) (Date of **October 8, 1998**) (9/22/03 IDS Ref. AG) and Pieper et al. (Piper, U.; Hayakawa, K.; Li, Z., Herzberg, O. "Circularly Permuted β -lactamase from *Staphylococcus aureus* PC1" *Biochemistry* **1997**, 36, 8767-8774) (9/22/03 IDS Ref. BI) and Moore et al. (Moore, J. T.; Davis, S. T.; Dev, I. K. "The development of β -lactamase as a highly versatile genetic reporter for eukaryotic cells" *Analytical Biochemistry* **1997**, 247, 203-208) and Maveyraud et al. (Maveyraud, L.; Pratt, R. F.; Samama, J.-P. "Crystal Structure of an Acylation Transition-State Analog of the TEM-1 β -Lactamase. Mechanistic Implications for Class A β -Lactamases" *Biochemistry* **1998**, 37, 2622-2628).

For *claims 63, 65 and 71*, the combined references of Michnick et al., Blau et al. and Pieper et al. teach all the limitations stated in the 35 U.S.C. 103(a) rejection above (incorporated in its entirety herein by reference), which renders obvious claims 63, 65 and 71.

The prior art teaching of Michnick et al., Blau et al. and Pieper et al. differ from the claimed invention as follows:

For *claims 66*, the prior art teachings of Michnick et al., Blau et al. and Pieper et al. differ from the claimed invention by not specifically reciting the use of SEQ ID NO:2 (i.e., TEM-1 β -lactamase).

However, Moore et al. and Maveyraud et al. teach the following limitations that are deficient in Michnick et al., Blau et al. and Pieper et al.:

For *claims 66*, the combined references of Moore et al. and Maveyraud et al. (see entire documents) teach the use of SEQ ID NO:2 (e.g., see Moore et al., abstract wherein TEM-1 β -lactamase is disclosed; see also Materials and Methods).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use SEQ ID NO:2 as taught by the combined teachings of Moore et al. and Maveyraud et al. with the complementation system as disclosed by Michnick et al., Blau et al. and Piper et al. because the combined references of Michnick et al., Blau et al. and Piper et al. explicitly state that a β -lactamase can be used for this purpose (e.g., see Blau et al., page 22, first full paragraph, “In one embodiment of the invention, the reporter subunits comprise an Enzyme ... Exemplary enzymes include ... β -lactamase”), which would encompass the β -lactamase disclosed by the combined references of Moore et al. and Maveyraud et al. Furthermore, one of ordinary skill in the art would have been motivated to use SEQ ID NO:2 because Michnick et al. state, “In designing a protein-fragment complementation assay (PCA), we sought [i.e., were motivated] to identify an enzyme for which the following is true: 1) An enzyme that is relatively small and monomeric [this is true for SEQ ID NO:2], 2) for which structural and functional information exists [this is true for SEQ ID NO:2], 3) for which simple assays exist for both *in vivo* and *in vitro* measurement [this is true for SEQ ID NO:2], and 4) for which overexpression in eukaryotic and prokaryotic cells has been demonstrated [this is true for SEQ ID NO:2]” (e.g., see Michnick et al., paragraph bridging columns 9-10). In addition, the combined references of Moore et al. and Maveyraud et al. state that TEM-1 β -lactamase is a good reporter because it provides “background free”

measurements (which is not the case for other systems like β -galactosidase) using a “variety of substrates which are efficiently cleaved” that can be “continuously monitor[ed] ... without destruction of cells” (e.g., see Moore et al., abstract). Finally, one of ordinary skill in the art would have reasonably expected to be successful because Blau et al. explicitly state that a β -lactamase can be used in complementation systems (e.g., see Blau et al., page 22, first full paragraph, “In one embodiment of the invention, the reporter subunits comprise an Enzyme ... Exemplary enzymes include ... β -lactamase”) and the combined references of Moore et al. and Maveyraud et al. further state that SEQ ID NO:2 [i.e., TEM-1 β -lactamase] is “extremely versatile in that it can be fused to other proteins and retain activity” (e.g., see Moore et al., abstract), which would encompass the “fusion” polypeptides used in the complementation systems of Michnick et al., Blau et al., and Piper et al. (e.g., see Michnick et al., claim 1 and Summary of Invention).

Response

8. Applicant’s arguments directed to the above 35 U.S.C. § 103(a) rejection were fully considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified from its original version to more clearly address applicants’ newly amended and/or added claims and/or arguments.

[1] Applicants argue, “None of the prior art references teach or suggest a fragment complementation system in which the N-terminal and C-terminal fragments of any enzyme are

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fused through the enzyme break points, much less a Class A β -lactamase. Michnick describes a protein-fragment complementation assay (PCA) using murine dihydrofolate reductase protein fragments (DHFR), in which 'Reconstitution of activity *only* occurred when both N- and C-terminal fragments of DHFR were coexpressed as *C-terminal fusions* to GCN4 leucine zipper sequences ...' See col. 5, lines 8-12 (emphasis added). In fact, Michnick's 'general description' of PCA is limited to systems in which 'the chosen fragments are subcloned, and *to the 5' ends of each*, proteins that either are known or thought to interact are fused ... Therefore, Michnick does not teach or suggest a fragment complementation system in which the N-terminal and C-terminal fragments of any enzyme are fused to the interactor domains through the enzyme break points" (e.g., see 12/22/05 Response, pages 7-9, especially bottom of page 8 and top of page 9).

[2] Applicants argue, "Blau also fails to teach or suggest a functional fragment complementation system having N-terminal and C-terminal Class A β -lactamase fragments fused through the enzyme breakpoints to the respective interactor domains" (e.g., see 12/22/05 Response, page 9, paragraph 2).

[3] Applicants argue, "Pieper does not teach or suggest fusion through an enzyme break point. In fact, Pieper fails to disclose fusion of an enzyme fragment to any interactor domain" (e.g., see 12/22/05 Response, page 9, paragraph 3).

[4] Applicants argue, "Moore and Maveyraud fail to cure the defects of Blau, Michnick and Pieper" (e.g., see 12/22/05 Response, page 9, last full paragraph).

[5] Applicants argue, "Even if the cited references disclosed all the elements ... there is no motivation provided in the prior art to modify the references fusion constructs to arrive at Applicants' invention. The cited references do not disclose any deficiency in the reported

constructs that would motivate one skilled in the art to fuse the fragments through the enzyme break point. In fact, the only motivation to modify the references fusion constructs is provided in Applicants' disclosure (e.g., see 12/22/05 Response, page 10, section 3).

[6] Applicants argue, "Assuming *arguendo* that the other basic elements of a *prima facie* case have been set forth, the cited references fail to provide a reasonable expectation of success. There is not indication in the prior art that the orientation of the references fragment fusion constructs may be reversed to arrive at an operable complementation system. As noted by Michnick, orientation of the fragments is important in the design protein complementation assays" (e.g., see 12/22/05 Response, page 10, section 4).

This is not found persuasive for the following reasons:

[1] The Examiner respectfully disagrees. The Michnick reference is not limited to systems where the interacting pair is fused only to the 5' ends of the enzyme fragments as purported. Applicants' cited passage merely refers to a description of figure 1 outlining method steps for a preferred embodiment. Michnick et al. state, "It is crucial to understand that these assays will only work if the fused, interacting proteins catalyze the reassembly of the enzyme" (e.g., see column 4, lines 38-40). That is, the Michnick reference, contrary to Applicants' assertions, does not require a particular type of fusion but, rather, any fusion that will allow the enzyme fragments to reassemble into an active form. Furthermore, Michnick et al. provide extensive guidance for selecting enzyme break-points that will insure the properly reassembly of the enzyme (e.g., see paragraph bridging columns 3 and 4, "One particular strategy for designing a protein complementation assay (PCA) is based on using the following characteristics ... 1) The fragments should result in subdomains of continuous polypeptide; that is, the resulting fragments

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will not disrupt the subdomain structure of the protein, 2) the catalytic and cofactor binding sites should all be contained in one fragment, and 3) resulting new N- and C-termini should be on the same face of the protein to avoid the need for long peptide linkers and allow for studies of orientation-dependence of protein binding”). Thus, the three factors cited above make clear that a particular type of fusion is not required and a person of ordinary skill in the art would not interpret it as such. In addition, the combined references of Blau et al. and Pieper et al teach the exact point at which a “class A” β -lactamase can be cleaved to form N-terminal and C-terminal fragments and yet still retain biological activity (e.g., see Pieper et al., abstract wherein the cp254 that was “cleaved in a loop remote from the domain interface” retained “similar” activity to the wild-type β -lactamase; see also cp228 construct, which shows rates that are 0.5-1% of the native enzyme against some substrates and 10-fold faster than the wild type against a third generation cephalosporin). Thus, to the extent that Applicants’ are arguing against the Michnick et al. reference alone, the Examiner notes one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Here, the combined references teach the exact position for fusion.

Finally, the Examiner notes that Applicants’ arguments are not commensurate in scope with the claims. Nothing in Applicants’ claims requires a particular type of fusion (i.e., 5’ or 3’). Applicants’ claims merely require that an N-terminal fragment and a C-terminal fragment be used regardless of how they are connected to the interactor domains.

[2] In response to applicant’s arguments against the Blau et al. reference individually, one cannot show nonobviousness by attacking references individually where the rejections are based

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on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). See [1] above.

[3] In response to applicant's arguments against the Pieper et al. reference individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). See [1] above.

[4] The Examiner respectfully disagrees. There are no defects in the combined references of Blau, Michnick and Peiper (e.g., see [1] above) and, as a result, no "curing" step is required.

[5] In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, one of ordinary skill in the art would have been motivated to use the a class A β -lactamase because Michnick et al. state, "In designing a protein-fragment complementation assay (PCA), we sought [i.e., were motivated] to identify an enzyme for which the following is true: 1) An enzyme that is relatively small and monomeric, 2) for which structural and functional information exists, 3) for which simple assays exist for both *in vivo* and *in vitro* measurement, and 4) for which overexpression in eukaryotic and prokaryotic cells has been demonstrated" (e.g., see Michnick et al., paragraph bridging columns 9-10), which are factors that all point toward the class A β -lactamase (see above). In addition, Pieper et al. demonstrate that a high

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degree of activity is retained upon fragmentation of the enzyme for constructs like cp254 and a range of activities for constructs like cp228 depending on the nature of the substrate (e.g., see Pieper, abstract, wherein the cp254 construct activity is disclosed as being “very similar” to the wild type; see also page 8773, column 1, Enzymatic Activity section). Finally, one of ordinary skill in the art would have reasonably expected to be successful because Blau et al. explicitly state that a β -lactamase can be used in complementation systems (e.g., see Blau et al., page 22, first full paragraph, “In one embodiment of the invention, the reporter subunits comprise an Enzyme ... Exemplary enzymes include ... β -lactamase”) and Pieper et al. provide explicit examples showing that a class A β -lactamase may be “functionally reconstituted” (e.g., see Pieper et al., abstract, cp254 and cp228 constructs). In addition, Michnick et al. state, “It should be understood that the instant invention is not limited to the PCAs presented here, as numerous other enzymes can be selected and used in accordance with the teachings of the present invention” (e.g., see also column 8, lines 18-21), which would encompass a β -lactamase.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

[6] Obviousness does not require absolute predictability. *In re Rinehart*, 531 F.2d 1048, 189 USPQ 143 (CCPA 1976); *In re Clinton*, 527 F.2d 1226, 188 USPQ 365 (CCPA 1976).

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Here, a person of skill in the art would reasonably have expected to be successful because Blau et al. explicitly state that a β -lactamase can be used in complementation systems (e.g., see Blau et al., page 22, first full paragraph, “In one embodiment of the invention, the reporter subunits comprise an Enzyme ... Exemplary enzymes include ... β -lactamase”) and the combined references of Moore et al. and Maveyraud et al. further state that SEQ ID NO:2 [i.e., TEM-1 β -lactamase] is “extremely versatile in that it can be fused to other proteins and retain activity” (e.g., see Moore et al., abstract), which would encompass the “fusion” polypeptides used in the complementation systems of Michnick et al., Blau et al., and Piper et al. (e.g., see Michnick et al., claim 1 and Summary of Invention). Furthermore, nothing in the cited passage by Michnick et al. indicate that the β -lactamase fusion wouldn’t work and, if anything, only reinforces the Examiner’s point that Michnick et al. is not limited to any particular type of fusion (e.g., see [1] above).

Accordingly, the 35 U.S.C. § 103(a) rejection cited above is hereby maintained.

Double Patenting

9. Claims 63, 65-67 and 71 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 63-65 of U.S. Patent Application No. 09/526,106 (referred to herein as ‘106) in view of Michnick et al. (U.S. Patent No. 6,270,964 B1) (Filing date is **February 2, 1998**) and Blau et al. (WO 98/44350) (Date of **October 8, 1998**).

An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examiner application claim is not patentably distinct from the

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reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1986).

Here, claims 63-65 of '106 recite polypeptides containing a first interactor domain, flexible polypeptide linker and an N-terminal β -lactamase fragment that fall within the scope of the first (or second) oligopeptide of the presently claimed invention that likewise contains an N-terminal fragment of a Class A β -lactamase, an interactor domain and a linker including the use of SEQ ID NO:2 and breakpoint at E197/L198 (also referred to as E172/L173 depending on the numbering convention) (e.g., compare claims 63-65 of '106 to claims 63, 65-67 and 71 of the currently claimed invention). The present application differs from '106 by further reciting a "second" oligopeptide to form a fully functional complementation system (i.e., the "first" + the "second" oligopeptide = complementation system). However, Michnick et al. and Blau et al. et al. teach the advantage of using both a "first" and a "second" oligopeptide to form a fully functional complementation system (e.g., see Michnick et al., claim 1; see also Blau et al., claim 1). Therefore, it would have been obvious to use a "first" oligopeptide as disclosed in the '106 patent with a "second" oligopeptide as taught by the combined references of Michnick et al. and Blau et al. et al. because complementation systems require "two" polypeptides in order to be useful (e.g., see Michnick et al., Summary of Invention, see also figure; see also Blau et al., Summary of Invention). One having ordinary skill in the art would have been motivated to make such a modification because Michnick et al. and Blau et al. et al. explicitly state that such systems are useful for β -lactamase polypeptides (e.g., see Blau et al., claim 21, "providing a

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reporter system comprising: a first component comprising a first low affinity reporter subunit, coupled to the first putative binding moiety, and a second component comprising a second low affinity reporter subunit coupled to the second putative binding moiety”; see also page 22, first full paragraph, “In one embodiment of the invention, the reporter subunits comprise an Enzyme ... Exemplary enzymes include ... β -lactamase”; see also page 14, lines 11-18; see also page 11, lines 21-24”; see also Michnick et al., paragraph bridging columns 9-10, “In designing a protein-fragment complementation assay (PCA), we sought to identify an enzyme for which the following is true: 1) An enzyme that is relatively small and monomeric [this is true for β -lactamase], 2) for which structural and functional information exists [this is true for β -lactamase], 3) for which simple assays exist for both *in vivo* and *in vitro* measurement [this is true for β -lactamase], and 4) for which overexpression in eukaryotic and prokaryotic cells has been demonstrated [this is true for β -lactamase]”), which would encompass the β -lactamase disclosed by ‘106. Furthermore, the claim 63 of ‘106 expressly states that the fragment is to be used in a complementation system, which would encompass the complementation systems disclosed by the combined references of Michnick et al. and Blau et al. Finally, a person of skill would have reasonably expected to be successful because Blau et al. explicitly state that a β -lactamase can be used in complementation systems that comprise two fragments (e.g., see Blau et al., page 22, first full paragraph, “In one embodiment of the invention, the reporter subunits comprise an Enzyme ... Exemplary enzymes include ... β -lactamase”).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

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10. Claims 63, 65-67 and 71 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 12 and 13 (especially claim 13) of copending Application No. 10/330,811 (Pub. No.: US 2003/0175836 A1) (referred to herein as '811). Although the conflicting claims are not identical, they are not patentably distinct from each other because the examined claims are either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1986). Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 63, 65-65 and 71 are generic to all that is recited in claims 13 of '811. That is, claim 13 of '811 falls entirely within the scope of claim 63, 65-67 and 71 of the present application or, in other words, claims 63, 65-67 and 71 are anticipated by claim 13 of '811. Specifically, [1] '811 discloses the α 197 ω 198 fragments (e.g., see claim 12) that fall within the scope of the Class A β -lactamase fragments disclosed in claims 63, 65-67 and 71 of the present application, [2] '811 discloses first and second leucine zipper moieties that fall within the scope of a first and second interactor domain as disclosed in claims 63, 65-67 and 71 of the present application and [3] both application also disclose the "reconstitution" of the enzyme (e.g., compare claim 1 in both applications).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

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11. Applicant's arguments directed to the above double patenting rejection were fully considered but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified from its original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

Applicants argue that the rejection should be held in abeyance until allowable subject matter is found (e.g., see 12/22/05 Response, page 11).

This is not found persuasive for the following reasons:

The provisional rejection will not be held in abeyance (e.g., see MPEP § 804 B. Between Copending Applications—Provisional Rejections, "The 'provisional' double patenting rejection *should continue to be made by the examiner* in each application as long as there are conflicting claims in more than one application unless that "provisional" double patenting rejection is the only rejection remaining in one of the applications."). Here, a double patenting rejection is NOT the only rejection remaining in one of the applications and thus the double patenting rejection is proper.

Accordingly, the double patenting rejection cited above is hereby maintained.

Allowable Subject Matter

12. Claim 72-74 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

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Applicant's amendment necessitated any new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.


Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon D Epperson whose telephone number is (571) 272-0808. The examiner can normally be reached Monday-Friday from 9:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (571) 272-0811. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jon D. Epperson, Ph.D.
January 1, 2006



ANDREW WANG
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600